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Editorial

Diabetes and macrovasculopthy: Double trouble!

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Diabetes is a chronic, degenerative, and non-communicable disease associated with a high prevalence of cardiovascular morbidity and mortality.[1,2] The most recent estimates of the International Diabetes Federation (IDF) indicate that 8.3% of adults i.e. 382 million people have diabetes, and the number of people with the disease is set to rise beyond 592 million in less than 25 years.[3] It is worrying that 175 million of cases currently unaware of their diagnosis and progressing towards complications. Moreover, with 80% of the total number affected living in low- and middle-income countries, where the epidemic is gathering pace at alarming rates.

According to IDF, approximately one-fifth of all adults with type 2 diabetes mellitus (T2DM) in the world live in the South-East Asia Region.[3] Current estimates indicate that 8.2% of the adult population, or 72.1 million people, have diabetes, 65.1 million of whom live in India. IDF also forecasted that the number of people with T2DM in the region will increase to 123 million by 2035, or 8.2% of the adult population. A further 24.3 million people have impaired glucose tolerance (IGT) , and this will increase to 38.8 million by 2035. The number of people with T2DM in India, Bangladesh and Sri Lanka make up 98.8% of the total for the region. A recent systematic review and meta-analysis conducted by Jayawardena *et al*.[4] on prevalence and trends of the diabetes epidemic in South Asia highlighted that urban populations had a higher prevalence of diabetes. Moreover, an increasing trend in prevalence of diabetes was observed in urban/rural India and rural Sri Lanka. A high epidemicity index was seen in Sri Lanka (52.8%), while for other countries, the epidemicity index was comparatively low (rural India: 26.9%; urban India: 31.3% and urban Bangladesh: 33.1%). It was also found that family history, urban residency, age, higher BMI, sedentary lifestyle, hypertension and waist-hip ratio were associated with increased risks of T2DM.

A sharp increase in the prevalence of T2DM has been observed in the SEA Region, both in urban and rural areas, which is mostly associated with lifestyles, high-fat diets and decreased exercise.[6] T2DM is the leading cause of CVD, renal disease, blindness and amputation.[1,3] Cardiovascular disease (CVD) is a major complication and the leading cause of early death among people with T2DM.[1] About 65% of people with T2DM die from heart disease and stroke. Adults with T2DM are 2-4 times more likely to have heart diseases or suffer a stroke than people without T2DM. High blood glucose in adults with T2DM increases the risk of heart attack, stroke, angina, and coronary artery disease. The clustering of vascular risk led to the view that CV risk appears early, prior to the development of T2DM.[1,6-9] Progressive nature of both T2DM and associated CV risk poses specific challenges at different stages of the life of an individual with T2DM.[1]

The complications of diabetic vasculopathy are commonly grouped into microvascular and macrovascular complications.[2] In diabetes, macrovascular complications are the commonest cause of morbidity and mortality and are responsible for a high incidence of vascular diseases.[1] Macrovascular diseases are traditionally thought of as due to underlying obstructive atherosclerotic diseases affecting major arteries.[2] The following pathological changes of major blood vessels occur which lead to functional and structural abnormalities in diabetic vessels include endothelial dysfunction, reduced vascular compliance and atherosclerosis.[2] Besides, advanced glycation end product formation interacts with specific receptors that lead to overexpression of a range of cytokines. Haemodynamic pathways are activated in diabetes and are possibly amplified by concomitant systemic hypertension. Apart from these, hyperglycaemia, non-enzymatic glycosylation, lipid modulation, alteration of vasculature and growth factors activation contribute to development of diabetic vasculopathy. This review focuses on pathophysiology and pathogenesis of diabetes-associated macrovasculopathy. Studies also demonstrated that following patient groups develop early manifestations of preclinical macrovasculopathy: newly diagnosed, never-treated individuals with T2DM/IGT and no traditional CV risk factors, and normoglycemic and normotensive offspring of parents with T2DM/IGT.[6-9] The presence of diabetes in parents constitutes increased risk of earlier onset of disease and its CVD complications in their offspring.[9] The studies on arterial stiffness in young people and offspring of diabetic parents are scarce, and limited study was reported in the literature on the offspring of patients with IGT.[9]

The modalities of treatment of diabetes includes: lifestyle modification (appropriate diet and exercise programs) and pharmacological intervention. Effective management of following reduce CV risks in diabetic patients: blood glucose, hypertension, blood lipid and blood hypercoagulability.[1]

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Increased obesity and decreased physical activity are strongly linked with an increased prevalence and incidence of T2DM.[3] Obesity is a predictor of both coronary heart disease and T2DM.[1] About 80%–90% of DM is attributable to excess weight. Limited studies conducted to assess the effect of intensive lifestyle intervention on CV outcome in T2DM.[1] Look AHEAD (Action for Health in Diabetes) study demonstrated that weight loss did not reduce the rate of CV events in overweight or obese adults with DM.[10]

Prolonged hyperglycaemia is a major factor in the pathogenesis of diabetic vasculopathy.[1,2] Observational studies[11,12] found positive correlations between measures of glycaemic control and CV outcomes; however, clinical trials[13-16] failed to show consistent beneficial effects on cardiovascular events. It was demonstrated that glycaemic control reduces the risk of microvascular complications among patients with DM, but its effect on CVD is uncertain.[17-19] Though the landmark UKPDS 34[13] showed protective effect on CVD, CV mortality, and all-cause mortality in T2DM patients, the large randomized, controlled trials[14,16,22] found conflicting results.

Patients with T2DM and blood pressure (BP) are always at increased risk of morbidity and mortality from CV events.[1] Diabetic macrovasculopathy can be improved by lowering BP with antihypertensive drugs. Though a number of randomized controlled trials showed adequate aggressive BP control improves CV outcomes,[20-21] but others[16] found no positive results.

Dyslipidemia also contributes substantially to CV complications in patients with T2DM.[1] A number of studies have shown that lowering LDL cholesterol reduces the risk of major vascular events diabetic patients. Randomized controlled trials[23] in T2DM have consistently shown that statins significantly reduce the risk of major primary and secondary CV endpoints but trials[24-26] of fibrate therapy have shown mixed results.

Atherosclerosis and vascular thrombosis are major contributors to diabetic vasculopathy.[1] Platelets play a significant role in increasing the risk of CVD. Currently, aspirin is at the centre of this research and is widely recommended for primary prevention of CV events. Major guidelines[27] recommended aspirin for primary prevention of CV events, however a number of trials[28-30] found that aspirin did not prevent a first cardiovascular event or death and recommended to continue aspirin for secondary prevention. However, other antiplatelet drugs (e.g. Clopidogrel) were also found to reduce the risk of CV events in DM patients.[31.32]

There are a number of research gaps in the area of diabetes and macrovasculopathy which creates opportunities for the scientist/researchers to conduct clinical trials: (i) lifestyle: effect of exercise and diet on quality of life, morbidity, and mortality, with a special focus on CV outcomes, (ii) glycaemic control: effective pharmacological approaches for the management of hyperglycemia which also affect CVD risk reduction, (iii) blood pressure: aggressive BP control may be the most important factor in preventing adverse CV outcomes, (iv) lipid profiles: routine use of combination therapy with fibrate and statin to reduce CV risk as compared with statin alone, and (v) antiplatelet therapy: clear benefit of aspirin in the primary prevention of major CV events in T2DM patients.

Diabetes mellitus has reached epidemic proportions worldwide. South Asians are known to have an increased predisposition for diabetes which has become an important health concern in the region.[5] It is evident that several modifiable and non-modifiable risk factors play an important role in the pathogenesis of diabetes among South Asians. Hence there is an urgent need for more research to develop preventive and curative strategies to prevent diabetic epidemic in the region. The relationship of various degrees of glucose intolerance and CVD required to be investigated by longitudinal studies in different ethnic groups.

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